Anthranoid laxative abuse – a risk for colorectal cancer?

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Abstract

Anthranoid-containing laxatives – aloe, cascara, frangula, and rheum – may play a role in colorectal cancer. This risk is particularly important in view of the wide abuse of self administered laxatives for chronic constipation. There are data on the genotoxic potential of anthranoids and there is evidence of a tumourigenic potential in rodents. A case report and clinical-epidemiological studies have evaluated the cancer risk in patients who have abused anthranoid laxatives over a long period. Pseudomelanosis coli is a reliable parameter of chronic laxative abuse (>9–12 months) and is specific for anthranoid drugs. In a retrospective study of 3049 patients who underwent diagnostic colorectal endoscopy the incidence of pseudomelanosis coli was 3·13% in patients without pathological changes. In those with colorectal adenomas, the incidence increased to 8·64% (p<0·01), and in those with colorectal carcinomas it was 3·29%. This lower rate was probably caused by incomplete documentation of pseudomelanosis coli in those with carcinoma. In a prospective study of 1095 patients, the incidence of pseudomelanosis coli was 6·9% for patients with no abnormality seen on endoscopy, 9·8% (p=0·068) for patients with adenomas, and 18·6% for patients with colorectal carcinomas. From these data a relative risk of 3·04 (1·18, 4·90; 95% confidence interval) can be calculated for colorectal cancer as a result of anthranoid laxative abuse.

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The main anthranoid containing herbal drugs that are used as stimulant laxatives are senna, aloe, cascara, frangula, and rheum. Their principal glycosidic ingredients and their known aglycosidic intermediates are listed in Table I. Moreover, danthrone (chrysazine; 1,8-dihydroxyanthraquinone) and purified sennosides A+B have been or are active ingredients of laxative drugs. These drugs are recommended for the short term treatment (one to two weeks) of acute constipation and as a purgative before diagnostic and therapeutic endoscopy.

Assessment of the current risk of anthranoid laxatives and their possible role in colorectal cancer has to consider the following:

(1) There is worldwide abuse of laxatives, self administered for chronic constipation associated with a high fat and low fibre diet;

(2) Data have accumulated on the genotoxic potential of anthranoids in bacterial and mammalian studies[1-8] (for a review see[9]);

(3) There is evidence of a tumourigenic potential for danthrone and 1-hydroxyanthraquinone in rodents[10-12];

(4) A case report[13] and clinical-epidemiological studies[14-16] in patients who have misused anthranoid laxatives over a long period should be considered in a final risk assessment for colorectal cancer in man.

Several health problems may arise from the uncontrolled long term abuse of self administered laxatives but this study focuses only on anthranoid laxatives and their relation to the development of colorectal cancer. The results of our own clinical-epidemiological studies, based on the coincidence of pseudomelanosis coli and colorectal diseases in patients undergoing endoscopy, are reported.

Clinical-epidemiological studies

Since a patient's recall of drug history over the years is an unreliable measure for determining the extent of laxative abuse, we endeavoured to correlate the incidence of pseudomelanosis coli with the endoscopic diagnosis of colorectal diseases. Pseudomelanosis coli is regarded as a more reliable indicator of chronic anthranoid laxative abuse of more than nine to 12 months.[17] The incidence of pseudomelanosis coli in patients undergoing endoscopy or at autopsy is reported to be between 1 and 5·9%.[17-22]

RESULTS OF A RETROSPECTIVE STUDY

Retrospective analysis of more than 3000 patients undergoing endoscopic control between 1981 and 1987 showed an incidence of 3·5% for pseudomelanosis coli. Table II shows the main diagnosis in a total of 3049 patients and the frequency of pseudomelanosis coli as a coincident factor. Patients with no abnormal changes in the colorectal mucosa (n=1151) showed a pseudomelanosis coli incidence of 3·13%. In those with inflammatory large bowel diseases (colitis; n=742) the incidence was only 1·89%, whereas in those with diverticuloses (n=321) it was 4·98%. In patients with adenoma (n=683) the pseudomelanosis coli incidence was high at

TABLE I Anthranoid containing herbal laxatives

Drug	Plant	Main ingredients	Intermediates
Senna	Cassia angustifolia Cassia acutifolia	Sennosides A+B	Rhein, rhein-anthrone
Aloe	Aloe ferox Aloe barbadensis	Aloines A+B	Aloe-emodin, aloe-emodin-anthrone
Cascara	Cascara sagrada Rhamnus purshiana	Cascarosides A+B, C+D	Aloe-emodin, aloe-emodin-anthrone, chrysophanol-anthrone
Frangula	Rhamnus frangula	Frangulines A+B, gluco-frangulines A+B	Emodin, emodin-anthrone
Rheum	Rheum palm	Sennosides A+B, aloe-emodin-glycoside, emodin-glycoside	Rhein, emodin, aloe-emodin

TABLE II   Results of the retrospective study

Diagnoses	Total	Pseudomelanosis coli	% Pseudomelanosis coli	p Value %
No abnormality	1151	36	3·13	–
Colitis	742	14	1·89	10·79
Diverticulosis	321	16	4·98	12·34
Adenoma	683	59	8·64	<0·01
Carcinoma	152	6	3·94	90·54
Total	3049	130	4·26	–

TABLE III   Age and sex distribution of patients included in the prospective study

	Sex		
Age (y)	Female No (%)	Male No (%)	Total No (%)
0–10	2 (0·3)	2 (0·4)	4 (0·4)
10–20	27 (4·4)	20 (4·2)	47 (4·3)
20–30	96 (15·5)	61 (13·0)	157 (14·4)
30–40	76 (12·3)	44 (9·3)	120 (11·0)
40–50	71 (11·5)	80 (17·0)	151 (13·9)
50–60	80 (12·9)	102 (21·7)	182 (16·7)
60–70	115 (18·6)	73 (15·5)	188 (17·2)
70–80	114 (18·4)	72 (15·3)	186 (17·1)
>80	38 (6·1)	17 (3·6)	55 (5·0)
Total	619 (100)	471 (100)	1090 (100)

8·64% but in those with colorectal carcinomas (n=152) it was 3·94% only.

Statistical evaluation of the data overall showed significant differences in the incidence of pseudomelanosis coli for all diagnoses (p<0·01%, χ^2 test). When differences were checked between diagnostic groups and patients with no abnormality there was a significantly higher pseudomelanosis coli incidence (p<0·01, according to the Fisher test) for adenoma bearing patients only.

RESULTS OF A PROSPECTIVE STUDY
A prospective study in 1095 patients who underwent endoscopy between October 1989 and March 1991 was conducted to check the results of the retrospective study. The age and sex of the patients included in the study are given in Table III.

The doctors undertaking the endoscopy were trained and instructed to document the endoscopic evaluation of pseudomelanosis coli in every case, even after detection of a malignancy. The incidence was verified by macroscopic and microscopic inspection. Table IV gives the results of the prospective study. In patients with no abnormal changes a pseudomelanosis coli frequency of 6·9% was detected, indicating more reliable documentation of this observation than in the retrospective study. In patients with inflammatory diseases the pseudomelanosis coli incidence amounted to 2·3%, and in those with diverticulosis to 9·1%. In patients with adenoma the incidence was increased to 9·8% (p=0·068),

TABLE IV   Results of the prospective study

Diagnoses	Total	Pseudomelanosis coli	% Pseudomelanosis coli	p Value
No abnormality	537	37	6·9	–
Colitis	221	5	2·3	<0·003
Diverticulosis	110	10	9·1	0·482
Adenoma	225	22	9·8	0·068
Carcinoma	59	11	18·6	<0·0008
Total	1095	77	7·0	–

and in those with carcinoma it was 18·6% (p=0·0008). Statistical evaluation of these data indicate a significantly higher incidence of pseudomelanosis coli in patients with tumours of the large bowel.

From these data a relative risk of 3·04 (1·18, 4·90; 95% confidence interval) for colorectal cancer can be calculated for patients who misuse anthranoid containing laxatives.

Analysis of incidences of adenoma, carcinoma, and pseudomelanosis coli was also performed in relation to sex and age groups. As expected, the carcinoma incidence in the under 50s (0·6%) was very much lower than that observed in the 50 to 70 years age group (7·5%) or the over 70 years group (11·6%). The incidences of adenoma in these age groups were 6·2, 31·5, and 32·2% respectively. The pseudomelanosis coli incidence also showed an increasing trend with age. It was 3·5, 8·1, and 12·3% respectively. The carcinoma incidences were essentially similar in men (5·2%) and women (5·7%) but the incidence of adenoma was slightly higher in men (23·6%) than women (18·2%). The incidence of pseudomelanosis coli was considerably higher in women (9%) than in men (4·5%).

In patients who had both tumour disease and pseudomelanosis coli, significant correlations were observed only in the cases of adenoma and pseudomelanosis coli incidence in men, and carcinoma and pseudomelanosis coli incidence in both men and those aged under 70 years. To obtain summarising estimates of the mutual effects of age and pseudomelanosis coli, and sex and pseudomelanosis coli, logistic regression analysis was applied. The logarithms of both adenoma and carcinoma quotients in all cases were found to be linear functions of age, sex, and pseudomelanosis coli. For adenomas there was a significant influence of age (factor 2·47), sex (factor 0·71), and pseudomelanosis coli (factor 4·57). For carcinomas there was a significant influence of age (factor 6·14), but neither a sex influence nor a mutual effect could be shown.

Discussion
Risk assessment for anthranoid laxatives is based on accumulated evidence for a genotoxic potential of some aglycosidic anthranoids and on in vivo carcinogenicity studies in rodents.[9] In a recently published case report[13] an association between danthrone exposure and human cancer was suggested. An 18 year old girl treated for five years with a laxative containing danthrone died from a leiomyosarcoma of the small intestine. In a clinical study[14] of 614 hospital patients with a history of laxative abuse and 1313 control patients, no higher incidence of cancer was found in the laxative abuse group. In a further analysis of 100 patients with colorectal carcinomas and 100 control patients, no higher intake of laxative drugs in the carcinoma group was detected.[15] A retrospective cohort mortality study[23] in 1975 dyestuff workers exposed to substituted anthraquinones showed no excess in total or cancer related mortality. Data from the Melbourne Colorectal Cancer Study,[16] which investigated 685 colorectal cancer cases and 723

age/sex frequency matched controls showed no higher risk related to laxative use. Self reported chronic constipation, however, together with high fat intake increased the relative incidence of colorectal cancer to 1·88 (95% confidence interval 1·26, 2·88). It is evident that this study did not differentiate between the intake of bulk laxatives and stimulatory laxatives of the anthranoid type.

The conclusions of our own clinical-epidemiological studies are based on the coincidence of pseudomelanosis coli and endoscopically verified abnormalities, assuming that pseudomelanosis coli is a reliable marker of chronic anthranoid type laxative abuse. This was confirmed by asking all patients with adenomas or carcinomas (n=33) included in the prospective study for their drug history. All patients except two acknowledged abuse of anthranoid laxatives for between 10 and 30 years. The discrepancy between the retrospective and prospective studies in the incidence of pseudomelanosis coli in colorectal carcinomas may be explained by incomplete documentation of pseudomelanosis coli during the endoscopic detection of a carcinoma, whereas adenomas are easily detected as depigmented white areas in a mucosa of brown-black pigmentation. The prospective study, however, indicated a clear cut association between pseudomelanosis coli and colorectal tumours in man.

Nevertheless, current retrospective and prospective clinical-epidemiological studies are contradictory, as chronic constipation per se together with dietary factors such as low fibre and high fat intake increase the risk for colorectal cancer in man. These confounding factors may largely be excluded by future case-control studies. At the moment, experimental data on genotoxicity and carcinogenicity in rodents alone allow us to assume a carcinogenic risk for anthranoid laxatives in man.

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